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CHANGES IN FACTORS THROUGH SELECTION

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MOST interesting of all the mutations that are now engaging the attention of students of mutation are those in which genetic factors or genes occur, or appear, whose most obvious action is to enhance or diminish some other more conspicuous character. These genes may be called specific modifiers. They do not differ from ordinary genetic factors in any essential respect, but, since their presence can not be detected, except when other factors are themselves producing some particular effect on the individual, it is convenient to give them a special designation.

For the correct interpretation of the results of selection, it is essential to have some means of finding out whether any effects that are produced are due to specific modifiers or to a change in the principal gene itself. For instance, there are several cases where a mutant character is known to be due to a single Mendelian factor, and selection has caused the character to change in the direction of selection, either plus or minus. Since the character is demonstrably due to a single factor the first conclusion that was drawn was that the change in the character *must* be due to a corresponding change in the factor that produces it. Such a conclusion may be fallacious, however, for the change may be due to the appearance during selection of specific modifying factors, or to their segregation if they were present at the start in a mixed stock. Until suitable tests were made, one interpretation was as valid as the other and without such test the wrong inference might be drawn.

It is obvious that it could never be shown that genetic factors do not change under the influence of selection if each time progress took place the results were ascribed arbitrarily to modifying factors. Conversely those who claim that progress comes about through modifying factors could never hope to establish their view so long as the possibility of the chief factor itself changing and producing the observed effects was open to discussion. But a modern technique has been worked out along several lines by means of which crucial evidence can be obtained that will make probable or even demonstrate whether the main gene or modifying genes are involved. Let us examine the ways in which a decision may be reached.

1. Starting with a mixed population in which the principal gene and one or more specific modifiers are present (the latter irregularly distributed amongst its members) and breeding in pairs along definite lines, we should expect to find in the first five or six generations that selection in a plus or minus direction would cause a definite change in the direction of selection and that then the process would slow down. This is the result that McDowell obtained when he selected flies for the number of bristles on the thorax, and it is in harmony with the view that modifying factors were present at first, irregularly distributed, and were sorted out by selection. If selection had really caused a principal gene for bristle number to change in the direction of selection it is not apparent why its progress should slow down and cease after a few generations, especially when selected in a minus direction. This argument gives results that are intelligible on the hypothesis that the change is not in the gene itself, but the method is insufficient to disprove that the gene changes; for, it might still be claimed that genes yield more at first to the treatment of selection and less later on.

2. It has been pointed out especially by East that the variability (spread) in the first hybrid generation (F_1) is often characteristically less than in the second (F_2), and this is expected on the theory of multiple factors, because the F_1 individuals are in their hereditary composition more likely to be uniform than the F_2 generation that results from the sorting of all the kinds of factors present in the F_1 generation.

3. The fact that there is less correlation between the "grade" of each F_1 individual and F_2 offspring than there is between each F_2 individual and its offspring (F_3) is expected on the multiple factor hypothesis, because all the differences of the F_1 individuals are not so probably due to genetic differences as are the differences between the F_2 individuals.

These and other correspondences between the expectation for modifying factors and the facts that are known in several cases create a strong presumption in favor of the theory, even though they do not pretend to demonstrate conclusively that modifying factors are present.

4. We may next turn to cases that furnish an actual demonstration that selection has produced its observed results through the isolation of genetic factors. This evidence is furnished by

linkage. Owing to the fact that in several cases linkage of factors is known, it may be possible to identify the presence in individuals of modifying factors when these are linked to visible ones. To run down modifying factors in this way is tedious, and to be entirely successful presupposes that all the great groups of linked genes are known and that within each a considerable number of loci are available. At present *Drosophila* is the only type which fulfills these requirements, and here at least five cases are known where the presence of specific modifiers has been demonstrated in the same way as all other genetic factors are demonstrated. Two examples may be given to show how such a demonstration was possible.

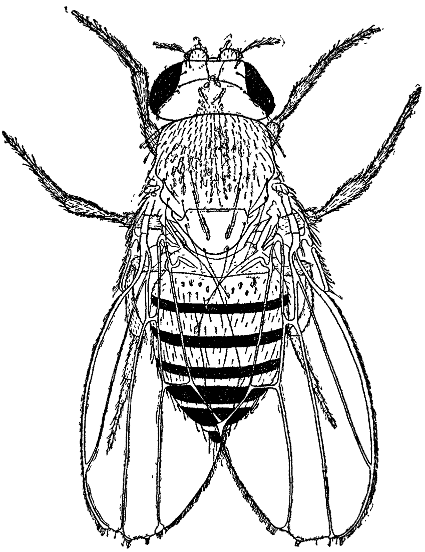

FIG. 1. A female fly (Drosophila melanogaster) from a mutant stock called notch in which the ends of the wings instead of being rounded (see Fig. 3A) are serrated. The factor producing the character is sex linked and dominant. It is also lethal, so that no males with notch appear because the male has but one X-chromosome. In the female, however, with two X's, the lethal effect of the notch gene in one X is counteracted by the normal allelomorph in the other X; but the dominant effect of the gene remains.

The general procedure is as follows: By appropriate matings to be described below, two kinds of individuals are produced that differ from each other in known respects, *i. e.*, in having different combinations of chromosomes. By testing in turn all the possible chromosomal combinations the presence of specific modifiers can be made out with certainty. An example will show in detail how the test is made. There is a dominant character known as notch wing, Fig. 1, whose gene lies in the sex chromosome. The character was found to be very variable in the original stock; a few flies in each generation that carry the factor have normal wings. By means of linkage experiments these normal-appearing notch females can be picked out from the real normals. By selecting such females for several generations the stock was changed to such an extent that more than half of the notch females had normal wings, and the rest had only faint indications of the notch. Females from the selected stock were bred out to males of another stock in which one of the third chromosomes contained a dominant factor (dichete) by means of which its presence could be identified. It was found that when both of the original third chromosomes were present the selected type of notch occurred, but when a dichete-bearing third chromosome was present the atavistic type of notch was present. The inference was that the modifier was present in the third chromosome and the inference became a demonstration when by means of similar tests for the other chromosome no modifier was found in them. The details of the test for the third chromosome alone are shown in Fig. 2, but the general nature of the test can be understood without need of this somewhat technical diagram.

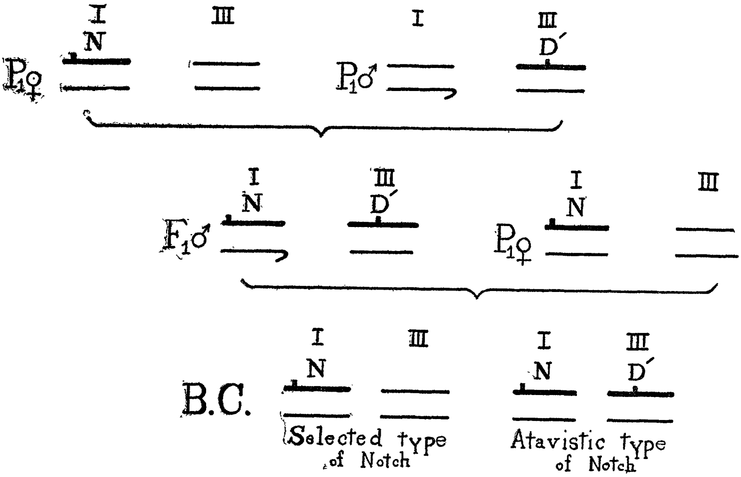

FIG. 2. Diagram to show how a specific modifier was located. The principal gene N for notch wing was carried in the first chromosome, I. A notch female (P_1) was mated to a male (P_1) that had a dominant gene for dichete bristles, D^1, in the third chromosome, III. A dichete son (F_1) was back-crossed to a notch female of stock (P_1). Two kinds of notch daughters are expected (BC), one having the original pair of third chromosomes should be like the original selected stock; the other with one of the original third chromosomes and its mate from the dichete grandfather. This female should be like the original (atavistic) type since the influence of the modifier in the third chromosome is dominated by its normal allelomorph in its mate, the dichete chromosome.

Another experiment made by Sturtevant in a different selection experiment was essentially the same. Only a preliminary statement has been made as yet by Sturtevant, and the following report is, with his permission, based on the complete account in press at present. He made use of a race of *Drosophila* called dichete, Fig. 3, *B*, characterized by fewer thoracic bristles on the average than in the wild type. In the wild fly there are four dorso-central and four scutellar bristles, Fig. 3, *A;* the former vary from 3 to 6, the latter vary less. In the dichete flies the bristle number for both groups of bristles taken together is from 3 to 7, five being the most common type.

Selected in the plus direction a race was produced with 6 as a mode and with a range from 4 to 8, selected in the minus direction the mode became 4 and the range from 1 to 6. Brothers and sisters were obtained that were alike in the first and in the third chromosomes, but different in the second chromosome. A comparison between them showed that a modifier was present in the second chromosome. In other words, selection for the number of bristles had changed the number, because a specific modifier for bristle number appeared in the course of the experiment in the second chromosome. Selection had produced its results by isolating a race in which the second chromosome pair contained a modifier.

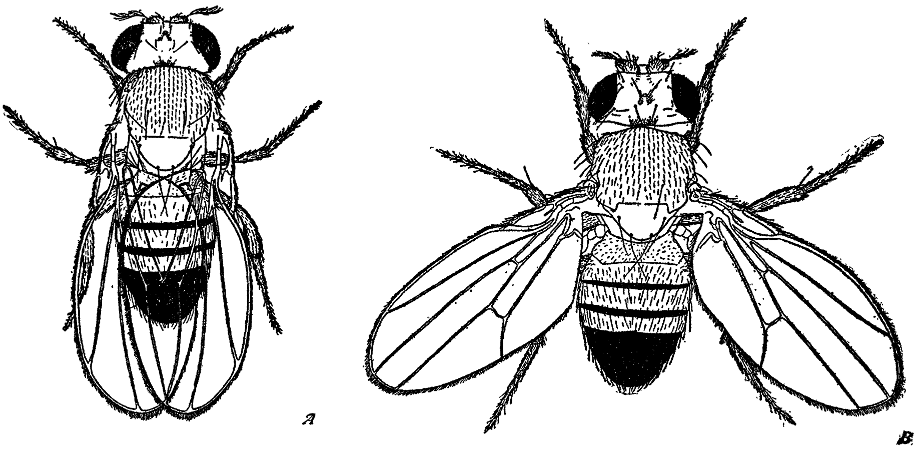

FIG. 3. A NORMAL MALE (Drosophila melanogaster), A, and a dichete male, B, that lacks certain bristles on the thorax. The gene is dominant and not sex-linked, but it is lethal in double dose. Hence all dichete flies (♂ and ♀) are heterozygous for the gene.

A third example could be given in which the specific modifier appeared in the same chromosome that carried the principal gene itself. No doubt cases will be found in which two or more specific modifiers are present. Their detection becomes then more difficult but can still be accomplished by the same sort of procedure.

An analysis of this kind brings to bear on the problem really critical evidence. Until equally cogent evidence can be obtained in other cases where it is claimed that mutant genes are modified by selection I do not think that this conclusion can be accepted.

MUTANTS OF MULTIPLE ALLELOMORPHIC GENES

Another one of the interesting and important discoveries in recent years has been the demonstration that more than one modification of the same gene may appear. The discovery is important not only because it shows the untenability of a current view that all mutants are due to losses of normal factors, but also because it shows that such mutant factors behave towards each other in the same way as the mutant gene behaves towards its normal gene (its "allelomorph") and consequently makes somewhat probable a view difficult to demonstrate otherwise that the normal gene is itself a gene like the mutant gene.

Multiple allelomorphs have now been found in a number of different forms. In mice the characters for black, yellow, gray with white belly, and house mouse gray form a series of allelomorphs. A mouse may have two of these at the same time but never more. If the genes are carried by the chromosomes and occupy identical locations in the chromosomes we can understand why only two can be present in the same individual, since there are only two chromosomes of each kind.

In rabbits there are three members of a series, black, albino and Himalayan. In corn, Emerson has described several allelomorphs that represent different grades of striping of the seed.

In one of the grasshoppers, *Paratettix,* Nabours has found about 13 allelomorphs affecting the color pattern of the body. It is not certain that this series is due to allelomorphic genes, for the same results would happen if the genes in question were in the same pair of chromosomes and no crossing over takes place. If, however, it turns out that these factors are allelomorphs the case is interesting because the types are found in the wild state.

By far the greatest number of series are in the fruit fly,[1] where their origin is known and where in consequence we are in a position to demonstrate from their mode of origin that they do not necessarily arise in that orderly sequence which their degree of development or expression might lead one to assume. The latter point, as will be shown, has an important bearing on our interpretation of what selection might be expected to do in cases where multiple allelomorphs arise or are present.

So far as the absence hypothesis is concerned, it is evident that if by absence we mean literally that mutant factors are absent genes, there could be but one kind of absence for each normal gene, hence there could not be a series of absences as the hypothesis of multiple allelomorphs assumes. If this is conceded and the hypothesis changed to mean that by absence only some part of a postulated organic molecule, or normal gene, is "lost," then a new point of view emerges. Suppose, for instance, the loss of a CH_2 group might give a new gene, the loss of another CH_2 group another gene, etc. On such an assumption several kinds of genes like several kinds of paraffines might be possible. But on the other hand the taking up of a CH_2 group, or a shift in position of two of the groups, might equally well make a new gene. There is at present no way of determining what kind of alteration produces a new allelomorph, hence the futility of insisting that such alterations must be losses rather than additions or alterations in position of parts of the gene. It need scarcely be added that there are no grounds for assuming that a deficiency rather than any other kind of alteration is the only change that will lead to a lessening of the development of the final product for which these genes are responsible. Fascinating as it might be to draw a parallel between the series of genes and the series of resulting multiple allelomorphs comparable to such series as the sugars or alcohols or paraffines with their corresponding graded differences in physical or chemical properties, such parallels are at present only in the speculative stage.

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[1] There are about 12 groups of multiple allelomorphs. The most extensive one is an octuple modification of the eye color involving white, eosin, cherry, etc.

The demonstration that multiple allelomorphs are modifications of the same locus in the chromosome, rather than cases of closely linked genes, can come only where their origin is known and at present this holds only for Indian corn and for the fruit fly. If each member of such a series has arisen historically from the preceding one in the series by a mutation in a locus closely associated with the locus responsible for the first, they would be expected to give the wild type when crossed; and as the proof of their allelomorphism turns on the failure of members of the series to show the atavistic behavior on crossing, it is necessary, as stated, to know how they arose. This may be made clear by the following illustration:

Let the five circles of Fig. 4, *A*, represent a *nest* of closely linked genes. If a recessive mutation occurs in the first one (line B *a*) and another in the second gene (line B *b*), the two mutants *a* and *b* if crossed should give the atavistic type A, since *a* brings in the normal allelomorph of *b* and *b* that of *a*. If a third mutation should occur in the third gene, it, too, will give the atavistic type if crossed to *a* or to *b*. Similarly for a mutation in the fourth and in the fifth normal gene. Now this is exactly what does *not* take place when members of an allelomorphic series are crossed—they do not give the wild type, but one or the other mutant type or intermediate characters. Evidently independent mutation in a nest of linked genes will not explain the results if the new genes arise directly each from a different allelomorph.

But suppose, as shown in Fig. 4 (line C) after a mutation had occurred in the first gene a new mutant, *b*, arose from a new gene, and from *b* a mutation arose in a third gene *c*, and *c* similarly gave rise to *d*; then *a* crossed to *b* will give *a* (or something intermediate if the heterozygote is an intermediate type). Likewise *c* crossed to *b* will give *b*, or *c* crossed to *a* will give *a*, etc. If mutant allelomorphic genes in a series such as *C a, b, c, d, e,* arise as successive steps, *i. e., Ca* to *Cb* and *Cb* to *Cc*, etc., then the hypothesis of closely linked genes would seem to be a possible interpretation, but if they do not arise in this way but by independent mutations from the wild type (or even from each other but not seriatim), then they must be due to mutations in the same gene; for, to assume that they are not, requires that, when the second mutation took place, both gene *a* and gene *b* mutated at the same time, and that when *c* appeared three genes mutated, when gene *d* appeared; when gene *e* five genes mutated at once, four of them bearing

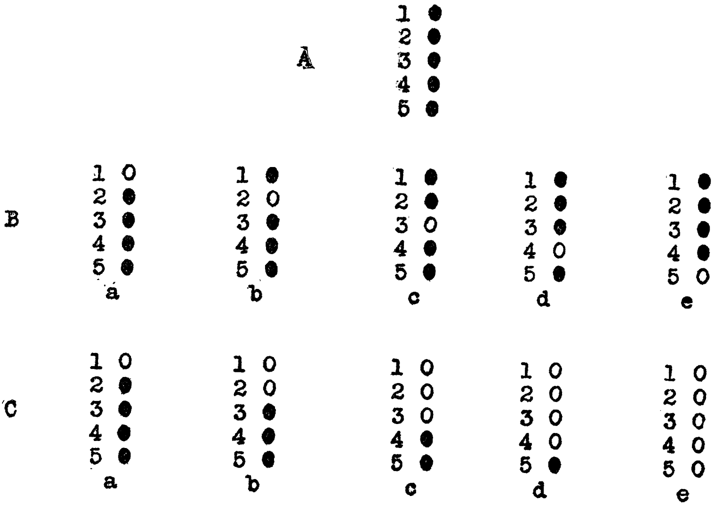

FIG. 4. Diagram of an imaginary "nest" of genes (A). In B the stages are independent mutations. If these stages *a, b, c,* etc., were crossed, the original type (wild type) of character is expected, since each stage would carry a normal allelomorph of the mutant gene in the other. In C the series of changes is indicated that might occur if *a* gave rise to *b* and *b* to *c*, etc.

mutant genes that have already arisen independently. Such an interpretation is excluded, since it is inconceivable, even in a readily mutating form like *Drosophila,* that five mutations could have occurred at the same time in distinct but neighboring loci. As has been stated the evidence from Drosophila shows positively that multiple allelomorphs arise at random.

The other evidence for multiple allelomorphs comes from an observation on Indian corn. Emerson has shown that when a race of corn having red cobs and red seeds is crossed to a race having white cobs and white seeds only the two original combinations appear in the second (F_2) generation, viz., plants with red cobs and red seeds and white cobs and white seeds. It follows that either a single factor determines that both cob and seed are red in one case and white in the other, or if the color of each part is due to a separate factor these must be so closely linked that no "crossing over" occurs. Other races, however, have different combinations of these characters, such as white cobs and red seeds, etc., or red cobs and white seeds, or white cobs and striped seeds, etc., and these combinations hold together, when crossed to each other or to either of those first named. Here again each set of characters that go together may be caused by one factor or by a set of factors so closely linked that they do not separate (cross over). Now the striped seeds with white cob sometimes mutate to red seeds and red cobs. The combination acts as a unit toward the other known combinations. Therefore a single factor must have caused the change, for, if not, mutation must occur in two (or more) closely linked factors for seed and cob color at the same time, which is highly improbable.

Only two members of a series of multiple allelomorphs can be present in any one individual, and in the case of genes carried by the sex chromosome only one can exist at a time in the sex that has only one of these chromosomes. In the individual with two mutant allelomorphs one of them replaces the normal allelomorph of the ordinary Mendelian pair. The two mutant allelomorphs behave towards each other in the same way as does the normal and its mutant allelomorph. It is doubtful whether we can conclude from this relation much more in regard to the relation of Mendelian pairs than we knew before,[2] although there is at least a sentimental satisfaction in knowing that the normal allelomorph can be replaced by a mutant one without altering the working of the machinery.

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[2] The substitution by crossing over really furnishes as good a demonstration of this point.

The linkage relation of each member of a series of multiple allelomorphs to all other genes of its chromosome is, of course, the same. While the theory of identical loci requires this as a primary condition it is not legitimate to use this evidence as a proof of the identity of the loci, because it is not possible to work with sufficient precision in locating genes by their relation to other linked genes to distinguish between identical loci and closely linked genes.

There is another question of some theoretical interest attached to the occurrence of multiple allelomorphs that calls for passing attention. If from the nature of the material mutation at a special locus were of such a kind that one step is essential before the next can be taken and if these genic steps give a progressive series of character changes, then it might appear to a person selecting for higher or lower grades of character in such a field that he was by his own efforts causing progress in the direction of his selection. In a certain sense he would be acting as an agent in hastening the possibility of the end result, because at each stage of progress he would breed as many individuals of the last stage reached as he could, and the number of individuals kept in stock would increase correspondingly the chance that some one of them would give the next mutant stage. Of course, the breeder here would be accelerating his end result not by controlling the conditions, so as to directly produce the change at will, but by making the chance that such an event would occur more probable by breeding a large number of individuals.

At present there is no evidence to show that multiple allelomorphic genes arise in the order of the development of the characters for which they stand. The few cases whose origin is known give exactly the opposite result. For instance, the octuple series of eye colors of *Drosophila,* grading from red to white, arose haphazard, so far as the amount of color shown by each mutant type is concerned. Mutation at this locus appears to take place more often than at any other locus, but not more often from the locus that has already mutated than from the wild type itself; in fact, more unit numbers of the series have appeared from the wild type, but this is expected if for no other reason than that more red-eyed flies pass under observation. It may be recalled in this connection that some other loci have been found that mutate to the same mutant type more often than do others, so that it may be that even some mutant loci may more frequently mutate than others or even than their own normal allelomorph. Since artificial selection is more likely to be followed up in cases where it is found to be giving results, it is not improbable that were such a condition realized it might easily mislead the breeder into supposing that his selection was producing progressive mutation changes, whereas he was succeeding because of a favorable situation that happened to fall into his hands.

While multiple allelomorphs present an extraordinarily interesting phenomenon of variation that has a profound bearing on our interpretation of the meaning of mutation, the facts indicate, so far as selection is concerned, that such allelomorphs fall into line with other mutants that supply selection with its material. The evidence shows in the most positive way that they originate as do other mutations, that the order of their appearance bears no fixed relation to the degree to which the character is displayed. Consequently they furnish selection with the same kind of material as all other mutations furnish. There is no evidence at present in favor of the view that selection has in itself any effect on the order of their appearance.